REMARKS

Applicant has amended the claims in order to expedite prosecution and advance the case towards issuance. In particular, Claims 38 and 43 have been amended to recite that the glucagon-like peptide 1 (7-36) amide agonist delays gastric emptying. Claims 41 and 46 have been amended to recite that the glucagon-like peptide 1 (7-36) amide agonist is glucagon-like peptide 1 (7-37). These amendments are fully supported by the application as filed, at pages 5-7 by way of example, add no new matter, and should not be construed as limiting the appropriate scope of protection provided by the doctrine of equivalents. Applicant responds below in detail to each of the rejections presented in the non-final Office Action mailed April 16, 1999.

I. CLAIMS 41 AND 46 ARE DESCRIBED

Claims 41 and 46 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient description. The Examiner states that there is no specific support for the species glucagon-like peptide 1 (7-36) and suggests amending the claims to recite glucagon-like peptide 1 (7-37).

In order to expedite prosecution and advance the case towards issuance, Applicant has amended the claims as suggested by the Examiner. Thus, this issue is now moot and

Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

II. CLAIMS 38-41 AND 43-46 ARE ENABLED

Claims 38-41 and 43-46 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling the use of any analog to glucagon-like peptide 1 (7-36) amide. The Examiner states that it would involve undue experimentation to determine which amino acid substitutions could be made without destroying glucagon-like peptide 1 (7-36) amide activity:

> Claims 38-41 and 43-46 recite the use of an analogue to GLP 1 (7-36) amide to treat Type I diabetes; however, the present specification fails to disclose any other peptide which has GLP 1 (7-36) amide activity in treating diabetes. In addition, the specification provides no guidance as to which of the 30 amino acids may be changed while GLP 1 (7-36) amide activity is retained. The total number of 30 amino acids is 3.4×10^{29}. The number of single amino acid substitutions is 600. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain GLP 1 (7-36) amide activity, and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo et al., (V), newly cited, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495:), it would require an undue amount of experimentation for one of skill in the

> art to arrive at the other 30 amino acid peptides that have GLP 1 (7-36) amide activity.

Applicant respectfully traverses the rejection to the extent that it may be held to apply to the claims as amended.

In order to enable a claimed invention, all that is required is to provide sufficient information that one skilled in the art can make and use the claimed invention. Thus, it is the law that an applicant need not describe every possible embodiment in order to obtain claims that would fully protect his or her invention. The PTO has itself recognized that limiting an applicant to the preferred materials in the absence of limiting prior art does not serve the constitutional purpose of promoting the progress in the useful arts. M.P.E.P. §2164.08(c).

Indeed, the concerns raised in the Office Action are of the type that were long ago rejected by the Court in In re Fuetterer, 138 USPQ 217 (CCPA 1963) (Rich, J.). There, speaking through Judge Giles S. Rich, co-author of the 1952 Patent Act and 43-year member of the CCPA and the Court of Appeals for the Federal Circuit, the court considered an appeal from a rejection of claims to a rubber stock for producing tire treads. The claimed rubber stock included "an inorganic salt" that was defined only by being "capable of holding a mixture of [a previously referred to] carbohydrate

and [a previously referred to] protein in colloidal suspension in water." Id. at 219. The Board had affirmed the rejection of the claim as "unduly broad." According to the Board, "Since the alleged novelty appears to reside in the result desired to be obtained by the salts, it is not proper to define the salt by what it is supposed to do rather than what it does." Id. at 221.

Judge Rich promptly disposed of this rejection as unsound:

> The desired result of appellant's invention is limiting the skidding of a tire tread stock on a wet surface. Appellant, in the claims before us, is not claiming this result. A myriad of alternative means for achieving this result can be easily thought of which would not require the particular combination of substances claimed by appellant. Insofar, therefore, as a "functional" claim may mean one which covers all means of arriving at the desired result, although the means by which such result is obtained is entirely different from that disclosed by the applicant, it is apparent that appellant's claims are not "functional."

Id. at 221 (emphasis added). Similarly, the result to be achieved by the use of the invention claimed by applicant in this case is the treatment of Type 1 diabetes. There are plainly other means for treating Type 1 diabetes (e.g., by the use of insulin) that do not require the particular means claimed by applicant.

It is well settled, furthermore, that patent applicants are not required to disclose every species that may be encompassed by their claims, even in an unpredictable art. In re Angstadt, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). Indeed, it is not even required that every embodiment in a disclosure be operative in order to be enabling under 35 USC 112, first paragraph. Atlas Powder Co. v. E.I. Dupont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Geerdes, 491 F.2d 1260, 180 USPQ 789 (CCPA 1974).

Judge Rich also stressed in In re Fuetterer that patent applicants must be able to obtain claims that adequately protect their inventions, even though some experimentation may be required to determine if a product or method falls within the scope of the claim. Judge Rich described Fuetterer's claim and the PTO rejection as follows:

> The rejection of the claims for "undue breadth" places particular emphasis on (1) an alleged "undue burden upon the public to determine what salts are suitable for obtaining the desired results" (emphasis ours), and (2) an alleged "undue [amount of] experimentation" required of those skilled in the art to determine those salts possessing the "function asserted" by the instant claims. The undue breadth rejection phase of the instant case appears in the following posture. Appellant has described his invention as comprehending the use therein of any inorganic salt capable of performing a specific function in a specific combination and he has disclosed specifically four such salts which are capable of performing this function. The examiner and the board, believing that not all inorganic salts are capable of performing this function and

> that one skilled in the art would not know offhand which inorganic salts are capable of so functioning, have rejected the claims as "unduly broad."

Id. at 222-223. According to Judge Rich, however, this was all "beside the point" and could not support the PTO's rejection:

> We find the arguments of the board and the examiner relating to experimentation necessary to determine the suitability of undisclosed salts to operate in appellant's claimed combination beside the point. Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination.

Id. at 223 (emphasis added). Likewise, applicant's invention in this case is not the discovery that certain compounds have glucagon-like peptide 1 (7-36) amide activity, but that such compounds will be useful in the treatment of people with Type 1 diabetes.

In In re Fuetterer, Judge Rich further emphasized that an applicant's claims may not be restricted so that they are easily avoided simply by identifying an undisclosed compound that will work:

> If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims

> should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure. The only "undue burden" which is apparent to us in the instant case is that which the Patent Office has attempted to place on the appellant.

Id. (emphasis added). Similarly, if others in the future discover other glucagon-like peptide 1 agonists aside from those set out in applicant's specification with the ability to slow gastric emptying and treat Type 1 diabetics, applicant will have no control over them per se (if the claims are limited to the subject matter the Examiner has indicated is enabled). Nevertheless, following In re Fuetterer, it is plain that under the law applicant's claims cannot be so restricted by the PTO that they can be avoided merely by using some compound not named in his disclosure.

The claims, as amended, recite methods of treating Type I diabetes by administering a glucagon-like peptide 1 amide agonist that delays gastric emptying. Here, there is no evidence that those skilled in the art could not readily make or test known or later-developed glucagon-like peptide 1 (7-36) amide agonists for their ability to delay gastric emptying and determine their suitability for the treatment of people with Type I diabetes. See, e.g., International Patent Publication No. WO 91/11457, attached hereto as Exhibit A, which describes various glucagon-like peptide 1 peptide

analogs (see page 4, line 33 - page 7, line 2) and International Publication No. WO 90/11296 attached hereto as Exhibit D, which describes various derivatives of glucagon-like peptide(See Summary of the Invention pages 5-7). There is no reason to believe that those skilled in the art could not test these and other glucagon-like peptide 1 (7-36) amide agonist compounds to evaluate utility in treating Type I diabetes patients. In view of the cases cited above, it would be improper to limit Applicant to use of preferred materials when such claims might be attempted to be avoided merely by using different agonists that could be readily made and tested given the information in the present application.

In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

III. THE SECTION 103 REJECTION IS IMPROPER AND SHOULD BE WITHDRAWN

Claims 38-47 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Gutniak et al. in view of U.S. Patent 5,424,286, D'Alessio et al. and Goth. The Examiner states:

> One of ordinary skill in the art at the time the invention was made would have been motivated to treat Type I diabetics with either GLP-1 (7-36) amide or GLP-1 (7-37) since both are known to show strong

> insulinotropic effects in vivo as taught by Gutniak et al., and use a subcutaneous route of administration since the physiological effects of GLP 1 (7-36) amide are insulinotropic, and the prior art teaches co-administration of insulin and GLP 1 (7-36) amide for their combined blood glucose reducing capabilities and Goth teaches that it is desirable to prolong the absorption of insulin by administering it subcutaneously. The results of the Gutniak et al., teachings, when viewed from the point of view of those skilled in the art (i.e. the '286 patent and D'Alessio et al.) would reasonably suggest treating Type I diabetics with GLP-1 (7-36) amide or GLP-1 (7-37). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicant respectfully traverses to the extent the rejection may be held to apply to the claims as amended.

A. No Teaching Or Suggestion Of Use Of An Agonist That Delays Gastric Emptying

As noted above, the claims as amended recite methods for treating Type I diabetes by administering a glucagon-like peptide 1 amide agonist that delays gastric emptying. None of the cited references, either alone or in combination (even though Applicant does not admit such combination is proper), teach or suggest the use of glucagon-like peptide 1 amide

agonists that delay gastric emptying as presently claimed to treat Type I diabetes.

B. No Motivation To Use Compounds To Treat Type I Diabetes

Contrary to the Examiner's assertions, one of ordinary skill in the art at the time the invention was made plainly would not have been motivated to treat Type I diabetes with either glucagon-like peptide 1 (7-36) amide or glucagon-like peptide 1 (7-37). Although glucagon-like peptide 1 (7-36) amide and glucagon-like peptide 1 (7-37) were known to show insulinotropic effects *in vivo*, this does not support the Examiner's conclusion that one of ordinary skill in the art may have been motivated to treat Type I diabetes with these compounds. As Applicant has previously explained, in Type I diabetes, insulin is deficient or completely lacking by virtue of the destruction of the patient's pancreatic beta cells (the cells that produce insulin). Thus, it would have been completely unexpected that an agent which was believed to be useful only because of its ability to potentiate insulin release could be useful in the treatment of people with Type I diabetes, who do not have the ability to produce sufficient insulin and who have no secretory response for glucagon-like peptide 1 (7-36) amide to amplify.

Indeed, the authors of Gutniak, et al. support this, for they concluded only that glucagon-like peptide 1 (7-36) amide may be useful in the treatment of patients with NIDDM (Type II diabetes mellitus) (Gutniak *et al.*, Abstract). They said nothing about the treatment of other kinds of patients and recognized that the data disclosed did not support the use of GLP-1 (7-36) amide for the treatment of Type I diabetes mellitus (IDDM). Their paper concluded, for example, only that:

> A better treatment for patients with NIDDM [Type 2 diabetes mellitus] who do not respond to sulfonylurea therapy would be one that decreases their requirement for insulin and therefore decreased the occurrence of hypoglycemia. Our study demonstrates that at least in the short term, the administration of GLIP decreases postprandial insulin requirements and plasma insulin concentrations in patients with NIDDM. Therefore, the peptide may have a role in the treatment of some patients with diabetes.

Gutniak *et al.*, at page 1321 (emphasis added). The treatment of Type I diabetes is neither disclosed under § 102 or suggested within the meaning of § 103, and, meaningfully, is not even mentioned in either the introduction or the conclusion to the Gutniak et al. paper.

C. The Cited References Teach Away From The Claimed Invention

The Examiner appears to be relying on only select portions of the Gutniak *et al.* article and other cited references in making a rejection, while ignoring other portions of the article and other cited references which do not support the Examiner's position. This is impermissible under the patent laws. See, e.g., In re Wesslau, 147 USPQ 391,393 (CCPA 1965) ("It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.")

Applicant notes that the cited references must be considered in their entirety, including disclosures that teach away from the invention. Given the Examiner's rejection and statement that the Gutniak, et al. article would suggest treatment of Type I diabetic patients, and in view of Applicant's explanation that the Gutniak, et al. article provides no such suggestion, Applicant thought it would be useful to provide the Examiner a copy of International Patent Application WO 93/187 86 ("the '786 application", attached hereto as Exhibit B). The '786 application names the lead author of the

Gutniak, et al. article, Mark Gutniak, as an inventor. In the '786 application, the "broadest aspect" of the invention is said to relate to the preparation of a medicament for use in the treatment of Type II diabetes. Page 4, lines 28-page 5, line 8. Thus, even the primary author of the Gutniak, et al. article has indicated that there was no suggestion to treat Type I diabetes.

Other patent applications also describe glucagon-like peptide 1 analogs only in relation to treatment of Type II diabetes, and fail to suggest treatment of patients with Type I diabetes mellitus. See, e.g., International Patent Publication No. WO 91/11457 (Exhibit A) and European Patent Application EP 0708 179 A3, attached hereto as Exhibit C. Thus, those skilled in the art would have been led away from use of such compounds to treat Type I diabetes.

D. The '286 Patent Would Not Be Accepted By One of Ordinary Skill in the Art

Neither the '286 patent nor the D'Alessio article supply what the Gutniak *et al.* article lacks. Thus, contrary to the Examiner's assertions, the results of Gutniak *et al.*, when viewed from the point of view of those skilled in the art, would not reasonably suggest treating Type I diabetes with glucagon-like peptide 1 (7-36) amide or glucagon-like peptide 1 (7-37). As noted above, the discussion of Gutniak *et al.* in

the '286 patent must be read in light of the entire Gutniak, *et al.* article and the entire '286 patent. When it is read in this manner, it is apparent that the Examiner's reading of the '286 patent mischaracterizes Gutniak *et al.*

The statement in the '286 patent that, "[Gutniak *et al.*] reasoned that since GLIP is the naturally active form found in humans after a meal, this peptide may aid in glucose regulation in IDDM and NIDDM," is not accurate. As explained in detail above, Gutniak *et al.* only concluded that glucagon-like peptide 1 (7-36) amide may be useful in the treatment of patients with NIDDM (Type II diabetes mellitus) and did not suggest that glucagon-like peptide 1 (7-36) amide could be used to treat patients with IDDM (Type I diabetes mellitus). Thus, the Examiner's reliance on the '286 patent is misplaced. Simply because the '286 patent says that Gutniak *et al.* reasoned that glucagon-like peptide 1 (7-36) amide may aid in glucose regulation in IDDM (Type I diabetes mellitus), does not make it so. The Gutniak *et al.* article does not contain any such statement.

E. The D'Alessio Article Would Not Be Accepted By One Of Ordinary Skill In The Art

Nor does the D'Alessio article support the Examiner's assertions. As noted above, both the entire D'Alessio article and the entire Gutniak *et al.* article must be considered when

examining the statements in the Introduction and Abstract of the D'Alessio article to which the Examiner refers. For example, after the language quoted by the Examiner, the D'Alessio article points out some of the deficiencies of the Gutniak *et al.* article:

> It has recently been reported that infusions of GLP-1 into diabetic subjects decreased the insulin dosage required to maintain euglycemia. Furthermore, type I diabetic subjects treated with GLP-1 during one step euglycemic, hyperinsulinemic clamps had 10-15% higher rates of glucose than during control studies, thereby suggesting that GLP-1 may promote glucose uptake in addition to augmenting insulin release. However, it cannot be determined from these data whether GLP-1 exerts an effect on insulin sensitivity, or if it promotes insulin-independent glucose disposition. Furthermore, because glucose disposal rates were studied only in diabetic subjects, it is not known whether their augmentation by GLP-1 occurs in healthy people, and this might comprise a physiologic response of the peptide.

D'Alessio at page 2263, column 2, first full paragraph (emphasis added).

F. Goth Adds Nothing Of Substance

Goth fails to cure the above defects. Goth merely states that protamine is sometimes added to insulin to form a suspension for subcutaneous administration. Goth, either alone or in combination with the other cited references, fails

to suggest subcutaneous administration of a glucagon-like peptide 1 (7-36) amide agonist, as presently claimed.

Thus, it is clear that when each of the items cited by the Examiner is considered as a whole, the Gutniak *et al.* article, either alone or in combination with the '286 patent, the D'Alessio article and/or Goth, neither discloses nor suggests the presently claimed compositions and methods.

Applicants thus request that this rejection be reconsidered and withdrawn.

CONCLUSION

For the foregoing reasons, applicants submit that the pending claims are in condition for allowance and seek an early Notice thereof.

Should any issues or questions remain, the Examiner is encouraged to telephone the undersigned so that they may be promptly resolved.

Applicant hereby petitions for a three-month extension of time pursuant to 37 C.F.R. §1.136. Please charge our Deposit Account 12-2475 for $435.00 for three-month extension of time.

If this amount is incorrect, please charge or Deposit Account for the appropriate amount.

Respectfully submitted,

Dated: October 18, 1999

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